

REMARKS

Claims 108-134, 139, 140 and 144-146 are cancelled herein without prejudice or disclaimer and Applicant reserves the right to pursue subject matter of these claims in another patent application. Applicant introduces new claims 147-184, which find basis in the claims as originally filed and in the specification throughout, and therefore add no prohibited new matter.

New claim 147 is independent and claims 148-184 depend directly or indirectly therefrom. Claim 147 is directed to a process for depositing a defined nanoliter volume of a 3-hydroxypicolinic acid (3-HPA) matrix at discrete locations on a substrate, resulting in a substrate with discrete spots having the matrix and no analyte. The process includes depositing a defined and controlled 0.2 to 20 nanoliter volume of a solution comprising the matrix, an evaporating solvent and no analyte. The resulting substrates are useful for matrix-assisted laser-desorption ionization (MALDI) mass spectrometric analysis.

In the Office action dated July 21, 2006, the Office rejected claims 108-134, 139-140 and 144-146 under 35 U.S.C. §103 for alleged obviousness in view of Hayes, Hancock and Zhang. The Office also rejected claims 144 and 145 for alleged indefiniteness under 35 U.S.C. §112, second paragraph.

Applicant respectfully submits the rejections under 35 U.S.C. §103 or 35 U.S.C. §112, second paragraph, are inapplicable to the new claims, as described hereafter.

The New Claims Are Not *Prima Facie* Obvious

Claimed matter is *prima facie* obvious only when a combination of cited documents (1) teaches or suggests all of the claimed elements, (2) the person of ordinary skill in the art was motivated to modify the document(s) as suggested in the Office action, and (3) there was a reasonable expectation of success. See MPEP 2142, et seq. The combination of Hayes, Hancock and Zhang fails to meet all three criteria.

1. The Combination Fails to Teach or Suggest All of the Claimed Elements

The combination of Hayes, Hancock and Zhang fails to teach or suggest a process for preparing a substrate that includes an array of spots having 3-HPA matrix and no analyte. Hayes does not teach or suggest processes of depositing 3-HPA because there is no mention of mass spectrometry and there is no mention of any matrix in the document. Thus, Hayes does not teach or suggest the claimed processes. The Office also has not established the apparatus discussed in Hayes can deliver defined and controlled 0.2 to 20 nanoliter volumes of 3-HPA, as specified in the pending claims. The lack of this showing is significant as Applicant found delivering volumes of 3-HPA matrix can clog piezoelectric apparatus components, the type of components addressed in Hayes (e.g., Applicant's specification, page 26, line 8). Thus, Hayes fails to teach or suggest the claimed processes.

Hancock does not cure the deficiencies of Hayes. Hancock, while mentioning 3-HPA in a listing of matrix types, does not address the claimed methods for preparing a substrate that includes spots having 3-HPA matrix and no analyte. Hancock states a matrix solution is mixed with the analyte, which results in regions containing a mixture of matrix and analyte, not spots having the matrix and no analyte. Please see, for example, Hancock at column 6, lines 23-26, column 10, lines 59-64, column 12, lines 32-35 and column 13, lines 39-41. Thus, Hancock fails to cure the defects of Hayes as it also does not teach or suggest features of the claimed methods.

Zhang does not cure the defects of Hayes and Hancock. Zhang discusses methods of depositing solutions containing matrix and an analyte on a substrate, not a solution comprising 3-HPA without an analyte, as specified by the claims.

Further, Zhang and Hancock teach away from the claimed methods. As noted above, Zhang specifies a solution of analyte and matrix are simultaneously deposited onto a substrate, and Hancock specifies matrix is added to analyte on the substrate. Accordingly, these two documents teach away from the claimed processes of preparing substrates that include spots having the 3-HPA matrix and no analyte. The combination of Hayes, Hancock and Zhang therefore fails to teach or suggest the claimed processes.

2. There Was No Motivation to Combine or Modify the Cited Documents

The Court of Appeals for the Federal Circuit (CAFC) in *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998) reversed a finding of unpatentability by the Board of Appeals on the basis there was no motivation to combine the documents cited for the rejection of Rouffet's claims. The Court identified three possible bases for motivation to combine documents.

The first listed basis, "the nature of the problem to be solved," is not found here as the pending claims are directed to processes for preparing substrates useful for MALDI mass spectrometric analysis and Hayes makes no mention of mass spectrometry, or any suitable matrix or any substrate. The stated objective of Hayes is to generate substrates having an array of probes useful for diagnostics (e.g., column 2, lines 36-39 and title), not for generating mass spectrometric substrates. The person of ordinary skill in the art therefore would not have combined or modified Hancock or Zhang with Hayes.

Further, Zhang is directed to analysis of polypeptides (i.e., neurotensin and substance P) and therefore a matrix solution different than 3-HPA, the latter of which is utilized for analysis of nucleic acids, was utilized (i.e., alpha-cyano-4-hydroxycinnamic acid). Paragraphs 4 and 5 of the Thomas Becker Declaration filed with the Office on October 14, 2005 (copy attached hereto) establishes protein/peptide matrix solutions have different properties than 3-HPA. Accordingly, there was no motivation to apply Zhang to the new claims.

The second basis, "the teachings of the prior art," is not found here either as there is no motivation provided by the documents themselves. As addressed above, Zhang and Hancock teach away from the new claims since they discuss methods for (i) depositing a solution comprising matrix and an analyte, or (ii) combining matrix with a deposited analyte, respectively. Accordingly, there was no motivation to apply Zhang or Hancock to the claimed processes.

The third basis is "the knowledge of persons with ordinary skill in the art." In order to apply this basis, the Court stated it would be necessary to "explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination" and concluded that "the Board merely

invoked the high level of skill in the field of the art. If such a rote indication would suffice to supply a motivation to combine, the more sophisticated scientific discovery would rarely, if ever, experience a patentable technical advance.” The CAFC further commented that the knowledge of persons of ordinary skill in the art may include certain references of special importance (i.e., that one or both of the cited documents is so well known that anyone in the art would be familiar with the documents). An example would be the famous Kholer and Millstein paper on monoclonal antibody preparations.

Here, the Office has not articulated the specific understanding or technological principal within the knowledge of one of ordinary skill in the art that would have led to combining or modifying the cited documents. The documents cited also do not rise to the level of importance that they can be deemed documents of special importance. Thus, there is no showing that it was within the level of ordinary skill in the art to combine or modify the cited documents and arrive at the claimed methods.

Accordingly, the person of ordinary skill in the art would not have modified or combined Hayes, Hancock and Zhang to arrive at the claimed processes.

3. “Obvious to Try” Is An Improper Rationale for the Outstanding Rejections

The Office’s modification of the cited documents is based upon an impermissible “obvious to try” rationale. The CAFC clarified it must be determined whether the prior art, and not Applicant’s disclosure, suggested to one of ordinary skill in the art that the claimed process should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical*, 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988).

The combination of Hayes, Hancock and Zhang does not teach or suggest the claimed processes, as addressed above. In addition, there was no reasonable expectation that the substrates useful for MALDI mass spectrometry could be successfully prepared. The Thomas Becker Declaration notes in paragraph 5 that research pertaining to matrix solutions utilized for peptide/protein MALDI analysis was not applicable to preparing substrates having 3-HPA matrix useful for nucleic acid analysis. It was not until the claimed substrates were generated using the methods and equipment described in the specification and then analyzed, that it was determined they could be successfully utilized

for reproducible mass spectrometric analysis (e.g., Thomas Becker Declaration, paragraph 5). Accordingly, the combination of Hayes, Hancock and Zhang provided no reasonable expectation that substrates having spots of 3-HPA useful for mass spectrometric analysis could be successfully produced, and therefore, the claimed processes are not obvious.

4. Impermissible Hindsight

Given the lack of a *prima facie* showing of obviousness based on the cited documents, Applicant is concerned the Office impermissibly asserted obviousness of the previously pending claims based upon the teachings of Applicant's specification. It has long been held that an obviousness rejection may not be founded upon the teachings of the specification and the use of hindsight (e.g., *In re McLaughlin* 170 USPQ 209 (CCPA 1971)). Applicant respectfully concludes the rejection in view of Hayes, Hancock and Zhang is based upon impermissible hindsight given the deficiencies of the rejections described above.

The New Claims Are Not *Prima Facie* Indefinite

The Office stated claims 144 and 145 were indefinite. This rejection is inapplicable to the new claims, and particularly new claims 162 and 163, as the latter specify the spot sizes are "defined by" two-dimensional square parameters. The specification provides basis for such square parameters, and the maximum surface area of a circular spot is defined by such parameters. For example, the maximum diameter of a circle is limited by each side of a square in which the circle resides (e.g., Applicant's October 14, 2005 response, page 7). Thus, the subject matter of the new claims is clear and not indefinite.

CONCLUSIONS

The new claims are not *prima facie* obvious because (1) the cited documents, in combination, fail to teach or suggest a process for preparing a substrate that includes spots having 3-HPA matrix and no analyte; (2) the documents cited are not properly combined or modified because Zhang and Hancock teach away from the claimed processes; and (3) the cited documents provided no reasonable expectation for successfully generating substrates useful for MALDI mass spectrometric analysis. And the new claims are not *prima facie* indefinite given the analysis above. Accordingly, Applicant respectfully requests withdrawal of the outstanding rejections and issuance of a Notice of Allowance.

In the unlikely event a pertinent document is separated from this submission and the Office determines that an extension and/or other relief is required, Applicant petitions for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-3473**.

Respectfully submitted,

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